



## Research paper

## Cortical thickness and volume reductions in young adults with current suicidal ideation

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## ABSTRACT

The extent to which observed differences in emotion processing and regulation neural circuitry in young adults with current suicidal ideation are paralleled by structural differences is unknown. We measured brain cortical thickness and gray and white matter volumes in 78 young adults aged 18–35: 35 with current suicidal ideation (SI) and 43 healthy controls (HC). The SI group, compared to HC, showed reduction in cortical thickness in the bilateral precentral gyri and diminished cortical volume in the left middle frontal gyrus. These regions are implicated in executive function, stress regulation, and emotion processing. We propose that these structural differences among the SI group could be contributing to suicidal thought patterns.

## 1. Introduction

Research in brain structural abnormalities of young adults with suicidal ideation may inform clinical interventions to prevent suicide. 36,000 individuals die from suicide annually (Nature, 2014). It is the 2nd leading cause of death among individuals ages 15–24 (Centers for Disease Control and Prevention, 2013), and is associated with major depressive disorder (MDD) (Bridge et al., 2006). Risk of attempting suicide among depressed individuals may be related to cortical structural abnormalities (Peng et al., 2016). We previously reported a decrease in brain volume in the right superior temporal gyrus in depressed adolescents with a past suicide attempt relative to healthy controls. This finding, however, was not present between depressed adolescents without history of suicide attempt and healthy controls, indicating a potential difference in cortical structure associated with suicidal behavior (Pan et al., 2015). Studies employing functional magnetic resonance imaging (fMRI) are also relevant for the investigation of neural mechanisms that may underlie suicide and depression. There are described functional differences in emotion processing, stress regulation, and emotion processing relative to healthy controls (Jollant et al., 2008; Pan and Phillips, 2014). We have found many existing functional differences in depressed patients with and without suicidal behavior (Pan et al., 2011, 2013a, 2013b; Chase et al., 2017; Just et al., 2017), and structural changes are equally important contributors to neurobiological models related to suicide. What remains unknown is how these functional differences are paralleled by structural abnormalities, which

could provide measures of neuropathophysiological processes underlying suicidal behavior that are more accessible than measures of neural function.

## 2. Method

After informed consent, 78 total adults with current suicidal ideation ( $n = 35$ ) and healthy controls with no personal or family history of psychiatric disorder or suicide attempt ( $n = 43$ ) participated in this study that was approved by the Institutional Review Boards of both the University of Pittsburgh and Carnegie Mellon University. Exclusion criteria included neurological disorders, anoxia history, head injuries, Wechsler verbal score  $< 80$  (Weschler, 1999), current use of sedative medication, pregnancy, ineligibility for magnetic resonance imaging (MRI), psychosis, substance misuse or positive urine drug/saliva alcohol screen. History of suicide attempt was assessed with the Suicide Intent Scale and Suicide History Form (Beck et al., 1974; Oquendo et al., 2003). Depression, anxiety, trauma, and suicidal ideation were assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2008), the Patient Health Questionnaire-version 9 (PHQ-9) (Kroenke et al., 2001), Adult Suicide Ideation Questionnaire (A-SIQ) (Reynolds, 1987), the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994), the Adult Spielberg Sate Trait Anxiety Inventory (STAI-T) (Spielberger, 1983), and the Adult Self Report (ASR) (Achenbach, 2003) respectively. All SI participants were medicated with antidepressants and/or mood stabilizers.

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Data was collected on a 3.0 Tesla Siemens Magnetom Verio scanner at the Scientific Imaging and Brain Research Center at Carnegie Mellon University with a 32-channel Siemens receive coil. T1-weighted magnetization prepared rapid gradient echo (MPRAGE) structural images of 176 1.0-mm sagittal slices were acquired during the scan session (repetition time: 1700 ms; echo time: 2.48 ms; inversion time: 900 ms; field of view: 256 mm; flip angle: 9°; matrix: 256 × 256). This scan used the Siemens turbo-flash sequence with a GRAPPA in-plane phase-encode parallel acceleration factor (i.e., iPAT factor) of 2. Total acquisition time was 5 min and 21 s.

Brain cortical thickness and gray and white matter volumes were measured using FreeSurfer 5.1 for Linux (<https://surfer.nrm.mgh.harvard.edu/>). The analysis included intensity normalization, registration, skull stripping, segmentation of subcortical white matter, tessellation of the gray matter and white matter boundary, and surface deformation. Topographical defects were automatically corrected and images were normalized and smoothed with a 10 mm FWHM kernel. According to the Desikan–Killiany atlas, FreeSurfer parcellates the cortex into 34 gyral-based regions-of-interest (ROIs) per hemisphere. For each of the 68 cortical parcellations, FreeSurfer then calculates the average cortical thickness and the cortical gray matter volume. Cortical thickness measures were computed as the distances between the gray/white matter boundary and the pial surface (Fischl and Dale, 2000). Cortical volumes were calculated from the surface mask (Fjell et al., 2009). Two, whole-brain surface-based analyses of covariance were completed in Qdec1.4 (FreeSurfer application) to examine the main effect of group on cortical thickness and volume, with age, gender, and total brain volume as covariates. Monte-Carlo simulation analyses were performed to correct for multiple voxel-wise comparisons in Qdec, and provide a cluster-wise significance threshold of  $p < 0.05$  for these analyses. Only effects with significant cluster-wise values after Monte-Carlo simulation are included. Coordinates are depicted as peak-coordinates within the MNI reference frame.

The FreeSurfer 5.1 process was manually checked, and no errors occurred. We also visually checked the cortical reconstruction of each subject for inaccuracies. No participants needed to be excluded based on motion, all participants had motion parameters under 2 mm.

To examine the nature of between-group differences in cortical thickness and volume, values were extracted from all cortical regions identified in the above analysis of covariance (ANCOVA). *Post hoc* pairwise, between-group independent *t*-tests were conducted on these extracted values. Significance thresholds for comparisons were  $p < 0.05$  (two-tailed) and Bonferroni-corrected for the two *post hoc* comparisons. Exploratory correlational analyses to examine relationships between any cortical thickness and volume abnormalities and clinical variables were completed in SPSS version 20.0.

### 3. Results (Table 1)

Groups did not differ significantly in age, ethnicity, and IQ score, but did differ by gender (77.1% female,  $X^2 = 3.87$ ,  $p = 0.049$ ), with a greater proportion of female participants in the SI group. This is also consistent with population studies that indicate higher rates of reported suicidal ideation in women than men (Hawton, 2000; Paykel et al., 1974). We accounted for this difference in gender ratio by including gender as a co-variate in the analysis. As expected, participants in the SI group were significantly more symptomatic than the HC group, and showed greater evidence of past maltreatment (CTQ scores,  $n = 23$  with past trauma in SI group). Within the SI group, 51.14% ( $n = 18$ ) reported a prior suicide attempt; past attempters had higher scores, compared to SI without a history of attempt, on self-reported depression (PHQ, Mean attempters =  $14.89 \pm 4.85$ ; Mean non-attempters =  $9.82 \pm 6.6$  [ $t = 2.59$  (34),  $p = 0.014$ ]) and current suicidal ideation (SIQ, Mean attempters =  $71.39 \pm 31.68$ ; Mean non-attempters =  $43.47 \pm 24.35$  [ $t = 2.90$  (34),  $p = 0.006$ ]).

#### 3.1. Cortical volume results (Fig. 1A)

One-way ANCOVA results revealed that participants with current suicidal ideation showed significantly reduced volume than the healthy controls in the left rostral middle frontal gyrus ( $F(1,76) = 4.63$ ,  $p = 0.04$  cluster level;  $x = -30$ ,  $y = 46$ ,  $z = 10$ , vertex = 55, cluster size =  $872.46 \text{ mm}^2$ ) from the whole brain analyses.

#### 3.2. Cortical thickness results (Fig. 1B)

One-way ANCOVA results revealed that participants with current suicidal ideation showed significantly reduced thickness than the healthy controls in the left precentral gyrus ( $F(1,76) = 4.63$ ,  $p = 0.035$  cluster level;  $x = -57$ ,  $y = 0$ ,  $z = 11$ , vertex = 4, cluster size =  $7376.11 \text{ mm}^2$ ) and the right precentral gyrus ( $F(1,76) = 6.63$ ,  $p = 0.012$  cluster level;  $x = 40$ ,  $y = -11$ ,  $z = 43$ , vertex = 19, cluster size =  $1468.38 \text{ mm}^2$ ) from the whole brain analyses.

Exploratory analyses between participants with current suicidal ideation and past trauma experiences ( $n = 23$ ) and the healthy control group ( $n = 43$ ) revealed similar cortical thickness findings as our full sample comparisons. One-way ANCOVA results revealed that participants with current suicidal ideation and past trauma showed significantly reduced thickness than the healthy controls in the left precentral gyrus ( $F(1,64) = 8.53$ ,  $p = 0.005$  cluster level;  $x = -57$ ,  $y = -1$ ,  $z = 11$ , vertex = 4, cluster size =  $6840.00 \text{ mm}^2$ ) and the right precentral gyrus ( $F(1,64) = 6.85$ ,  $p = 0.011$  cluster level;  $x = 40$ ,  $y = -11$ ,  $z = 43$ , vertex = 19, cluster size =  $1820.51 \text{ mm}^2$ ). There were, however, no significant group differences in cortical volume between participants with current suicidal ideation and past trauma and healthy controls.

Post-hoc analyses revealed no significant within group differences in brain thickness and volume in the SI group when comparing suicide attempters ( $n = 18$ ) to non-attempters ( $n = 17$ ). There were also no significant within group differences in brain thickness and volume when comparing those in the SI group who experienced trauma ( $n = 23$ ) to those who did not ( $n = 12$ ). Exploratory analyses showed no significant relationship between depression (ASR, PHQ-9), anxiety (STAI-T) and trauma scores (CTQ), with thickness/volume in the suicidal ideation group, using a statistical threshold of  $p < 0.05$ .

## 4. Discussion

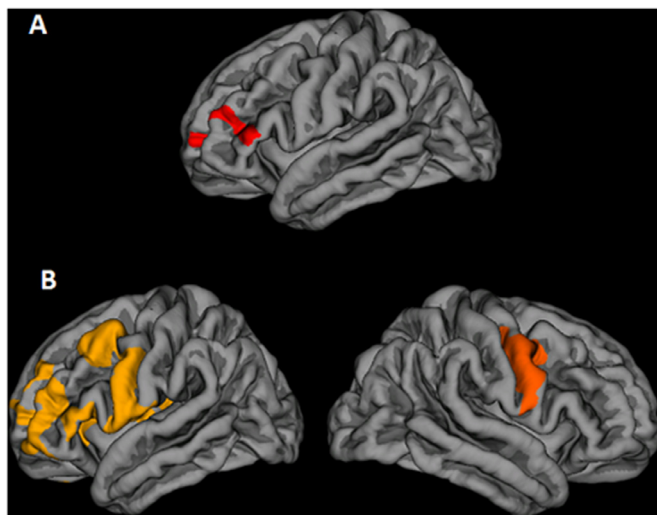
We found decreased cortical volume in the left rostral middle frontal gyrus and reduced thickness of the bilateral precentral gyri in the SI group compared to HC. The frontal gyrus is most often involved in executive function and regulation of behaviors during stressful situations; these cognitive abilities, however, have been shown to be dysfunctional among suicidal and depressed patients (Wang et al., 2008). Other studies have shown decreases in frontal brain volume in depressed non-remitted patients compared to healthy controls (Ide et al., 2015; Hoogenboom et al., 2013; Koolschijn et al., 2009), which also predicts a higher probability of non-remission of depressive symptoms (Korgaonkar et al., 2015). Further evidence shows smaller bilateral frontal cortical gray matter volumes in suicidal adult female patients compared with healthy control subjects (Monkul et al., 2007). Our findings of decreased brain volume and thickness in frontal cortical regions may help explain the reported cognitive rigidity and dysfunctional executive decision-making during stressful situations among depressed suicidal patients (Marzuk et al., 2005). Furthermore, the absence of any significant relationship between this cortical thickness/volume abnormality and measures of present depression and anxiety severity, and past trauma in the SI group suggests that abnormally reduced cortical volume in the left rostral middle frontal gyrus and reduced thickness of the bilateral precentral gyri may be potential trait markers of suicidal ideation.

Taken together, these findings may contribute to emotional

**Table 1**  
Demographic information, clinical variables, and statistics for all questionnaires in the SI and HC groups.

		SI (n = 35)	HC (n = 43)	Statistic (t-test unless stated)	p value
Gender	Male	8	19	$\chi^2 = 3.87$	0.049
	Female	27	24		
Mean age (years)		24.77 (S.D.: 5.54)	22.07 (S.D.: 2.83)	$\chi^2 = 19.75$	0.18
WASI (IQ)		119.60 (S.D.: 11.01)	120.63 (S.D.: 9.29)	0.44	0.66
PHQ		12.43 (S.D.: 6.23)	0.46 (S.D.: 1.14)	12.35	>0.001
ASIQ		57.83 (S.D.: 31.33)	2.18 (S.D.: 4.62)	11.51	>0.001
CTQ		51.11 (S.D.: 19.23)	30.91 (S.D.: 7.37)	6.34	>0.001
STAI-T		48.74 (S.D.: 5.47)	46.69 (S.D.: 3.46)	2.01	0.05
ASR subscales:					
1. Anxious/ depressed		21.91 (S.D.: 6.44)	4.40 (S.D.: 4.07)	14.63	>0.001
2. Withdrawn		6.74 (S.D.: 3.19)	1.47 (S.D.: 1.45)	9.69	>0.001
3. Somatic complaints		7.54 (S.D.: 4.97)	1.21 (S.D.: 2.07)	7.59	>0.001
4. Thought problems		6.11 (S.D.: 2.83)	1.21 (S.D.: 1.42)	9.95	>0.001
5. Attention problems		13.63 (S.D.: 5.70)	4.47 (S.D.: 3.49)	8.72	>0.001
6. Aggressive behavior		9.94 (S.D.: 5.08)	2.37 (S.D.: 2.40)	8.66	>0.001
7. Rule breaking		4.31 (S.D.: 3.23)	1.58 (S.D.: 1.68)	4.81	0.014
8. Intrusive		2.06 (S.D.: 1.81)	1.84 (S.D.: 1.98)	0.51	0.613
9. Internalizing problems		36.20 (S.D.: 10.43)	7.07 (S.D.: 6.12)	15.37	>0.001
10. Externalizing problems		16.31 (S.D.: 8.75)	5.79 (S.D.: 4.61)	6.81	>0.001
11. Total problems		89.00 (S.D.: 23.82)	24.49 (S.D.: 16.64)	14.04	>0.001

Demographic information and clinical variables: SI: suicide ideators, HC: healthy controls; WASI (IQ): Wechsler Abbreviated Scale of Intelligence, PHQ: Patient Health Questionnaire; SIQ: Suicidal Ideation Questionnaire; CTQ: Childhood Trauma Questionnaire; STAI-T: Spielberger State Trait Anxiety Inventory; ASR: Adult Self Report. Of the 35 patients, 31 were diagnosed with major depressive disorder (MDD), 21 were diagnosed with general anxiety disorder (GAD); 6 with bipolar I or II, 4 with borderline personality disorder, 2 with post-traumatic stress disorder (PTSD), and one each with cerebral folate deficiency, post-partum depression, anorexia, Tourette's disorder, obsessive compulsive disorder, Asperger's disorder, and attention deficit disorder. One patient was trans-gender (female to male). All SI participants were medicated, typically with antidepressants and/or mood stabilizers.



**Fig. 1.** (A) Diminished cortical volume in the left middle frontal gyrus in young adults with suicidal ideation compared with a healthy control group ( $p < 0.05$  corrected) co-varying for age, gender, and total brain volume (displayed on QDEC's pial cortical surfaces). Left rostral middle frontal gyrus (red):  $x = -30$ ,  $y = 46$ ,  $z = 10$ ; cluster: 872.46; vertex: 55;  $HC > SI$ ,  $p = 0.04$ ,  $F = 4.63$ . Only effects with significant cluster-wise values after Monte-Carlo simulation are included. Coordinates are depicted as peak-coordinates within the MNI reference frame. (B) Diminished cortical thickness in the bilateral precentral gyri in young adults with suicidal ideation compared with a healthy control group ( $p < 0.05$  corrected) co-varying for age, gender, and total brain volume (displayed on QDEC's pial cortical surfaces). Left precentral gyrus (yellow):  $x = -57$ ,  $y = 0$ ,  $z = 11$ ; cluster: 7376.11; vertex: 4;  $HC > SI$ ,  $p = 0.035$ ,  $F = 4.63$ . Right precentral gyrus (orange):  $x = 40$ ,  $y = -11$ ,  $z = 43$ ; cluster: 1468.38; vertex: 19;  $HC > SI$ ,  $p = 0.012$ ,  $F = 6.63$ . Only effects with significant cluster-wise values after Monte-Carlo simulation are included. Coordinates are depicted as peak-coordinates within the MNI reference frame. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

dysregulation and poor decision making, which are risk factors for suicidal behavior. Some limitations to the study include sample size, which was relatively modest, with further study in larger samples indicated. In addition, we did not have any non-suicidal psychiatric controls, so that findings may not have been specific for suicidal ideation or behavior. Further studies are also needed to assess whether cortical volume and thickness differences influence response to treatment. In summary, our findings are the first to show cortical gray matter volume and thickness reductions in key cortical regions important for emotion processing, executive function, and stress regulation among young adults currently contemplating suicide. A goal for future studies should be to determine the extent to which structural abnormalities, specifically decreases in cortical thickness and volume in frontal regions, are specific to ideation or suicidal behavior relative to psychiatric controls, and predict future suicide risk.

### Contributors

Study planning: Just, Pan, Brent.

Participant recruitment/data collection: Segreti, Pan, Brent.

Data analysis: Segreti.

Writing report: Segreti, Chase, Just, Brent, and Pan.

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### Conflicts of interest

Dr. Brent receives royalties from Guilford Press, has or will receive royalties from the electronic self-rated version of the C-SSRS from ERT, Inc., is on the Editorial board of UpToDate, is a reviewer for Healthwise, is on the board of the Klingenstein Third Generation Foundation, and receives honoraria for presenting at Continuing Medical Education

events. None of the other authors declare any financial or other conflicts of interest that might have biased the work.

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